Roche

Pharmaceuticals

2004N-0133
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
U.S.A.

Basel, July 8, 2004
Re: Comments for the re-examination of 21 CFR Part 11 (2004N-0133)

Dear Madam, Dear Sir,

On behalf of F. Hoffmann-La Roche Ltd, we would like to thank you for the opportunity to provide comments for the re-examination of 21 CFR part 11.

Roche is a leading healthcare company with a uniquely broad spectrum of innovative products. Our products and services address prevention, diagnosis and treatment of diseases, thus enhancing patient well-being and quality of life. The company employs around 65,000 people and sells its products in over 150 countries.
The focus of Roche is not solely the diagnosis and treatment of manifest disease. The integrated healthcare approach is increasingly offering ways of identifying and targeting diseases early, when their damaging effects can still be prevented. Arranged in two operative divisions, our global mission today and tomorrow is to create exceptional added value in healthcare. These two units are Pharmaceuticals and Diagnostics.

The Roche comments to Docket No. 2004N-0133 are structured to contain:

- The presentation of the cancelled 21 CFR part 11 meeting of June 11, 2004
- The answers to the questions as raised in the Docket Notice

Thank you for considering our comments for the re-examination of 21 CFR part 11.

Yours sincerely,

F. Hoffmann-La Roche Ltd

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2004N-0133

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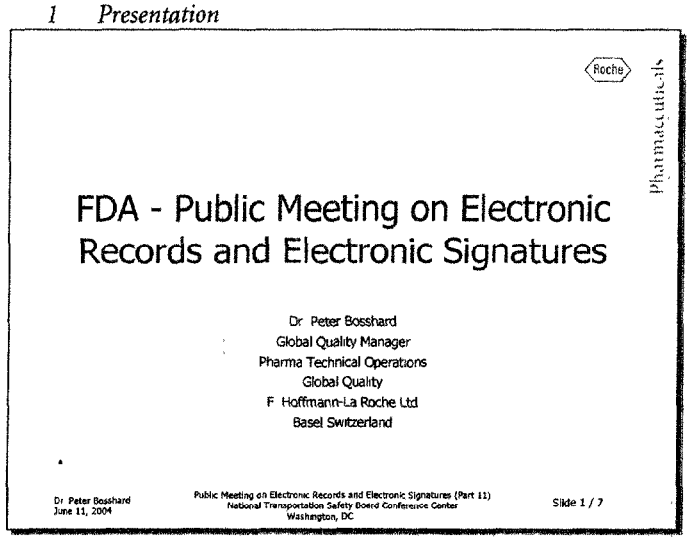
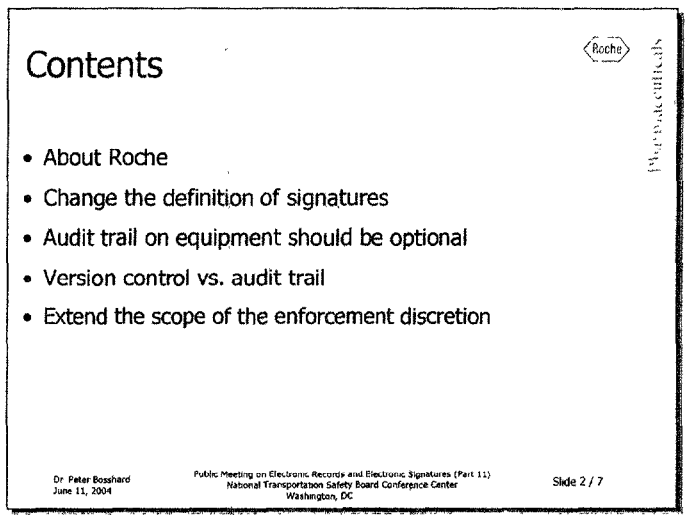
1 Presentation

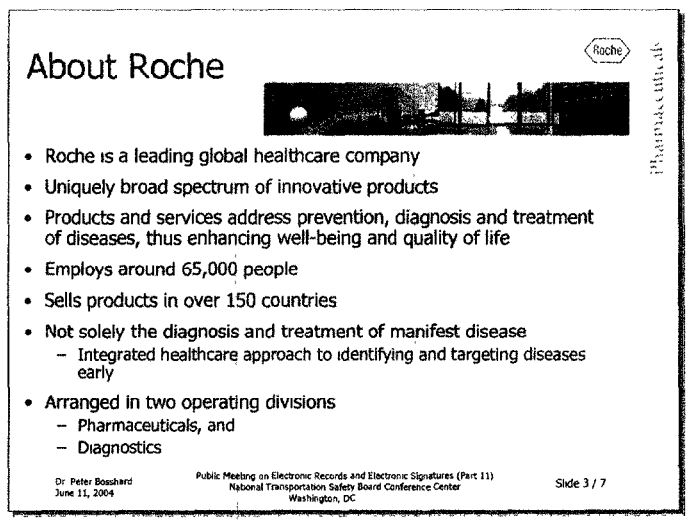


This slide is a short introduction of the speaker.

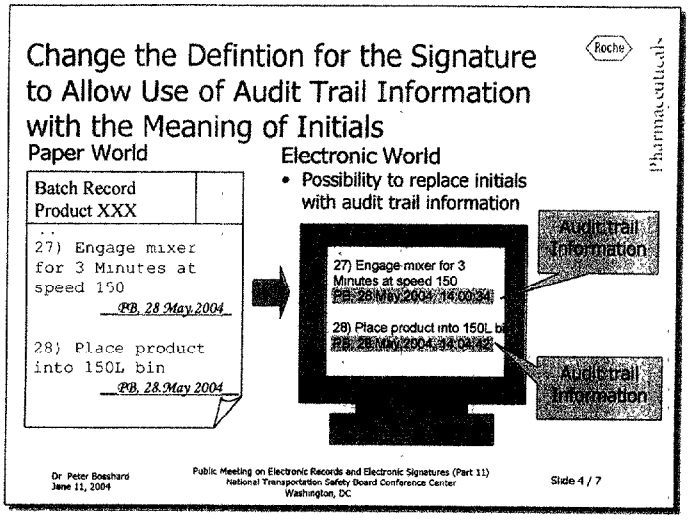
My name is Peter Bosshard. I am working in the Global Quality department of Pharma Technical Operations of F. Hoffmann-La Roche, Basel, Switzerland. I contribute as subject matter expert in Electronic Records and Signatures to the interpretation of the regulations, the establishment of internal guidance, training, advice and enforcement in self inspections.



This slide gives the outline of the items that are addressed in the presentation. A special comment to this slide is that we very much appreciate the withdrawal of the former guidelines for electronic records and signatures. In addition we hope very much that the items covered by the enforcement discretion of the Guideline, *Scope and application of 21 CFR part 11*, will be considered for the revision of 21CFR Part 11.



This is a short presentation of Roche that is publicly available on the internet. [Source: http://www.roche.com/home/company.htm]



In the paper world there is a clear distinction between initials and signatures. Individual process steps are usually confirmed with initials. These initials do not have the importance of signatures but they serve only to confirm that certain actions were performed. For example in a batch record we find numerous initials.

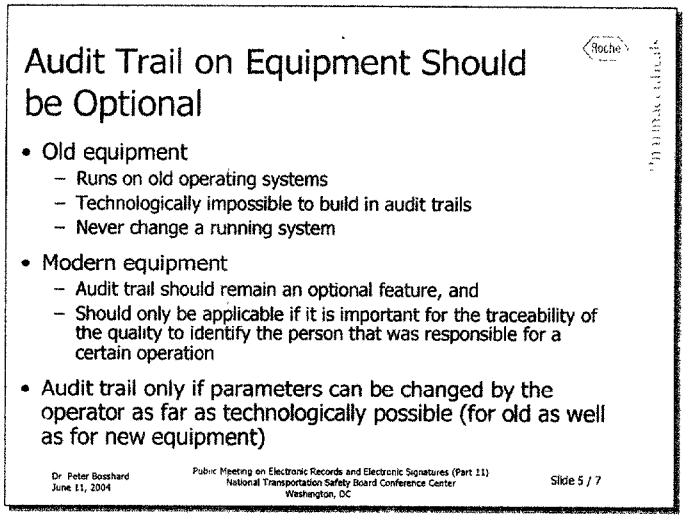
If this paper system were transformed into an electronic system, theoretically all the initials would need to be replaced with electronic signatures [11.3(b)(8)].

In practice this is not feasible, because numerous operations need to be performed in a timely manner and an extensive User ID/Password entry dialogue would conflict with the processes requirements. Even a simplified entry of only the password would not be feasible.

This clumsy requirement hinders the implementation of an electronic system in the production environment and many other places.

If the audit trail that captures this information were used as analogous to initials in paper systems, it would be encourage much more the change from a paper system to an electronic system.

We would appreciate if the definition for signatures in section 11.3(b)(8) could be modified in a way that audit trail information would be sufficient for this kind of confirmation initial.

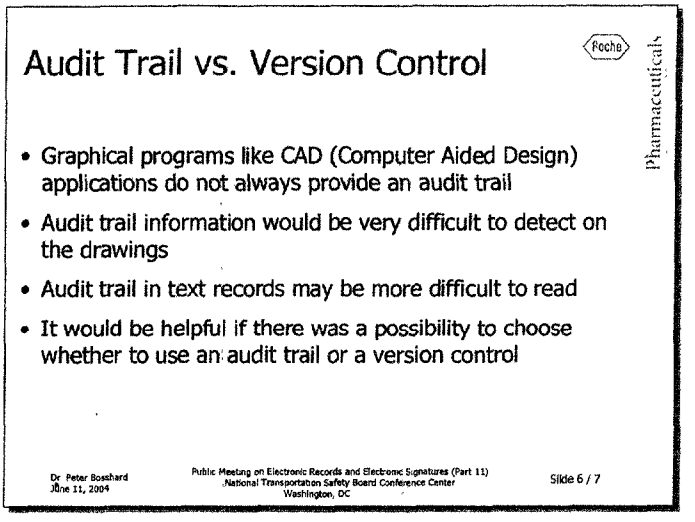


The content of this slide is similar to the concept in the specified enforcement discretion that if there is a risk assessment, systems could operate without an audit trail. We would like to emphasize here that an audit trail should be optional, and only be applied for data that is relevant for the traceability of the product quality.

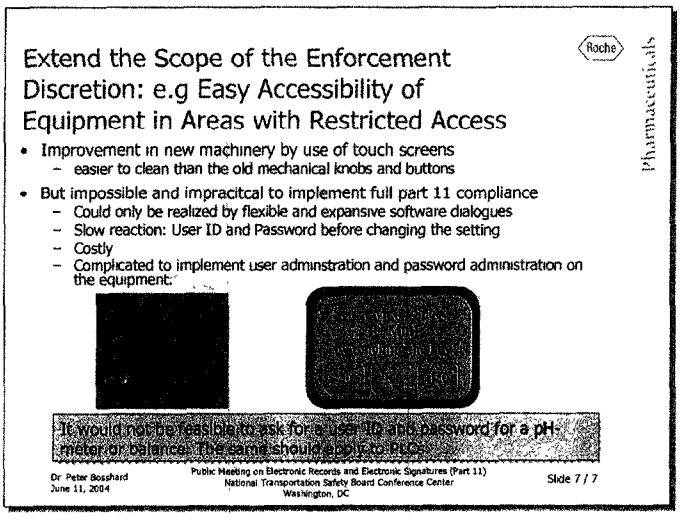
Currently, there is a lot of discussion in the various forums that an audit trail is necessary for any "direct impact" system. Direct impact systems are those systems that are assessed to have a direct influence on the product quality.

This is often technically not feasible, specifically for equipment that is used in various industries and not only in the pharmaceutical industry.

It should therefore be possible to run process equipment without audit trail.



If adequate version control of records is maintained, an audit trail should not be necessary as long as there is no explicit requirement to keep drafts in the relevant predicate rules.



More and more process equipment used in restricted areas contains microprocessors and touch panels as interface to the operator. These panels are used for such simple operation as to switch a machine on or off. These panels have the advantage in comparison with traditional electric switchboards that they are easier to clean and have less probability of contamination.
Part 11 should not apply to such equipment features because it would not be feasible to enter user ID and password, and to institute a complete user administration for simple operations. In simple equipment like mixers or washing machines, the time used to unlock the equipment could even lead to a negative impact on quality because an important operation might be delayed.

2 Answers to the questions as posed in the Federal Register Notice of April 8, 2004 (Page 18591-18593)

We are happy to give our statement on the very detailed questions that you had published in the above notice in the Federal Register. We appreciate that the industry has an opportunity to help with their comments to improve part 11.

This section contains statements for all the questions that were published in the above notice. The numbering follows the numbering of the notice.

2.A.1 Comments on FDA's interpretation of the narrow scope of part 11 records

We fully agree on the narrow scope of part 11records. Where computers are used to create paper records, the corresponding electronic records should be non regulated electronic records (NER), as specified in the scope and application guidance. We would appreciate if part 11 could be revised to reflect this.

2.A.2 Comments on whether revisions to definitions in part 11 would help clarify a narrow approach and suggestions for any such revisions.

Such a revision could help indeed, provided that it is also aiming to reduce the efforts invested in formalistic areas. This includes the definition for the handwritten signature (section 11.3(b)(8)) that should be modified in a way that the mass of initials and authorizations that are used in a paper environment for traceability of the identity of the operator can be performed in an electronic environment as audit trail information rather than signatures. In addition in some countries initials are not equivalent to handwritten signatures in the legal system. Therefore this definition should change.
Other definitions that should be reconsidered would be removal of closed (section 11.3(b)(4)) and open systems (section 11.3(b)(9)), and a modification of the definition of an electronic record (section 11.3(b)(6)) to include only regulated electronic records (RER).

2.A.3 Comments on the need for clarification in part 11 regarding which records are required by predicate rules and are therefore required to be part 11 compliant.

It would aid compliance to have clarification regarding the records that are required by the predicate rules and that must therefore be part 11 compliant. Because there are differences in requirements among the predicate rules (ie, GLPs, GMPs, GCPs, medical devices, etc.), it would be helpful to have the required records listed by the predicate rule to which they refer. In addition, some records are explicitly required in the regulations and other records may be implicit requirements based on having the evidence (documentation) to show that a particular requirement is met.

2.B Comments regarding Part 11 Subpart B—Electronic Records

2.B.1 Comments on whether there are other areas of part 11 (others than (validation, audit trail, record retention, and record copying) that should incorporate the concept of a risk-based approach, detailed in the part 11 guidance (e.g., those that require operational system and device checks).

There are indeed other areas including access controls. Some very reliable older equipment and PLC devices still have no other possibility than a key to lock the switch cupboard in order to limit access. It should be possible to trust in the operators that have physically a very limited access anyway to the production area.
Where either technical controls do not exist or in using them it would impede the process, it should be possible apply a risk based approach for:

- Discerning of changes(section 11.10(a))
- Protection of records(section 11.10(c))
- Access control (section 11.10(d))
- Sequence enforcement (section 11.10(f))
- Authority checks (section 11.10(g))
- Device checks (section 11.10(h))
- Use of appropriate controls over systems documentation (section 11.10(h)), as this is often difficult to verify for commercially available computerized equipment used in production.

It would be helpful to clarify in the part 11 revised regulation more explicit details regarding the risk-based approach to part 11.

2.B.2 Is additional clarity needed regarding how predicate rule requirements related to subpart B can be fulfilled?

Yes. Specifically when it comes to the predicate rules this clarity is needed. It would be preferred to speak instead of predicate rule of direct, indirect, and no impact records. Records that are required by the predicate rules sometimes have no direct impact on the quality of the pharmaceutical product. E.g. the 21CFR 211.34 "Consultants" demands that: "... Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide."
Whether an electronic record is classified as a RER or an NER (Non-regulated Electronic Record) should not be determined by the predicate rule alone but by the fact that a record is necessary for traceability of quality of a pharmaceutical product. The pharmaceutical company should be able to determine if an electronic record is a RER or an NER.

2.B.3 Should the requirements for electronic records submitted to FDA be separate from electronic records maintained to satisfy predicate rule requirements?

Yes. As these records are for a completely different purpose, have different requirements regarding confidentiality and archiving, and have no direct impact on the product quality, there should be separate requirements.

2.B.4 Should part 11 continue to differentiate between open systems and closed systems?

No. This differentiation does not help to use the right method in the right place. The only differing requirement between open and closed system is the procedures and controls needed for open systems. These procedures, "...designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation ... include ... document encryption and use of appropriate digital ... signature standards ..." might also make sense for closed system.

2.B.4.1 Should we retain the validation provision under Sec. 11.10(b) required ensuring that a system meets predicate rule requirements for validation?

Even though the predicate rules for GMP 21CFR211 do not explicitly require that computerized systems used in the production of pharmaceutical products should be validated, this validation is generally performed. The validation provision should be retained since computer validation has been an FDA requirement for GxP systems for many years, and it reinforces this requirement by being included in part 11. However, sometimes the validation activities are given the name qualification. Therefore you might consider extending the scope to include also qualification as an option.

2.B.4.2 Are there any related predicate rule requirements that you believe are necessary to preserve the content and meaning of records with respect to record copying and record retention? What requirements would preserve record security and integrity and ensure that records are suitable for inspection, review, and copying by the agency?

Preservation of records in the GMP area is already required according to 211.80(c). However, when it comes to records such as the validation documentation of a computerized system, we suggest that these can be destroyed as soon as the last product that was produced with the validated equipment has reached its shelf life plus one year in analogy to the batch documentation.

2.B.4.3 Should audit trail requirements include safeguards designed and implemented to deter, prevent, and document unauthorized record creation, modification, and deletion?

No. This is not feasible. Simple measures, such as not installing a tool on the equipment to modify the audit trail should be sufficient. In addition it would be inconsistent to provide enforcement discretion for the audit trail and then ask for additional security measures to be included in the audit trail later on. In addition the audit trail should be considered as no direct impact record.

2.B.4.4 Should part 11 be modified to incorporate concepts, such as configuration and document management, for all of a system's software and hardware?

No. This requirement would not be feasible. Some suppliers that sell both to companies within the scope of 21CFR11 and companies outside of the scope of 21CFR11 do not apply these standards. It is not possible to exclude major suppliers of standard operating systems and applications from pharmaceutical companies.

In addition, such requirements would make it practically impossible to program simple tools such as spreadsheets.

2.C Should part 11 address investigations and follow-up when these security breaches occur?

No. Again, some major suppliers that deliver to other industries besides the pharmaceutical industry would have some difficulties to fulfill this requirement. Some old reliable software also has some difficulties to fulfill the requirement as spelled out in Section 11.10(d) that requires that system access be limited to authorized individuals. However, it does not address the handling of security breaches when an unauthorized individual accesses the system.

2.D Additional questions for comment

2.D.1 What are the economic ramifications of modifying part 11 based on the issues raised in this document?

The money used to fix old systems could be used for new technologies. New technologies such as Process Analytical Technologies (PAT) would certainly profit.

More clarity would also facilitate application of the new part 11 for suppliers, consultants, the pharmaceutical industry and the agency inspectors.

2.D.2 Is there a need to clarify in part 11 which records are required by predicate rules where those records are not specifically identified in predicate rules? If so, how could this distinction be made?

Yes. However, it is doubtful whether the predicate rules alone are a good guidance. The predicate rules do not always specifically require records for those instances where the need for records is obvious e.g. validation of computerized systems. In other places predicate rules require records for operations that have no direct impact on the quality of the drug product or health service. (e.g. 211.34 see above). Therefore this distinction should be made in a way that clearly highlights the impact on the pharmaceutical quality.

2.D.3 In what ways can part 11 discourage innovation?

With the requirements of part 11 some very simple activities were made very complicated such as the use of a spreadsheet in the laboratory. Some laboratories stopped using spreadsheets because it was not easy to realize all the requirements of part 11 for the spreadsheet applications due to the technological limitations of the spreadsheet software. This can pose a higher risk to the correctness of the results because the traceability of wrong entries or operations is more difficult without a spreadsheet. Additionally, new technologies such as PAT, which produce high amounts of data, are hindered by the restrictive data retention requirements.

2.D.4 What potential changes to part 11 would encourage innovation and technical advances consistent with the agency's need to safeguard public health?

Technical innovation would be encouraged if 21CFR11 would allow a risk based approach for all controls depending on the impact on the pharmaceutical product.

2.D.5 What risk-based approaches would help to ensure that electronic records have the appropriate levels of integrity and authenticity elements and that electronic signatures are legally binding and authentic?

The risk based approach should focus on the impact of the record. Signatures should only be applied when necessary and not on every item where in a paper environment only initials are required.

2.D.6 What are stakeholder concerns in regards to modifications made to legacy systems in use as of August 1997?

If the modification changes the architecture or business processes, the legacy status should be lost. If the modification was only a bug fix or enhancement, e.g. new printer driver, then the legacy system status should remain. Legacy Systems should include systems that were constructed before August 1997 regardless of when they were brought into operation. If the deadline for legacy systems is rigidly based on the day of being brought into operation we will face inconsistent treatment of equipment. If two identical pieces of equipment were installed on the first of Jan 1997 and the second in Jan 1998 then different standards would be necessary for the same system.

2.D.7 Can the use of risk mitigation and appropriate controls eliminate concerns regarding legacy systems?

Yes. More important than the date of construction of the system is the impact on product quality. Risk assessment should be applied on legacy systems and the corresponding upgrading of the system should be made based on the technically available solutions.

2.D.8 Should part 11 address record conversion?

Yes. Such guidance would be helpful. Such a conversion statement should specifically allow for transformation of records in order to enable archiving in paper, microfilm or in a different electronic format. Such conversion might lead to the loss of information and capability, for example online checking of an electronic signature might be lost or recalculation may no longer be possible. It should be possible for a manufacturer to use a risk assessment to decide that recalculation, sorting or other features of the original record are no longer necessary and transformation of an active document to a historic record should be possible. Such conversion should be allowed by the new part 11.

2.D.9 Are there provisions of part 11 that should be augmented, modified, or deleted as a result of new technologies that have become available since part 11 was issued?

Yes, In the interest of PAT, it should be possible to delete large quantities of raw data that is not

necessary once a certain process step is terminated. It should be possible to keep only the consolidated results as far as reported in the batch record.